

Treating Pain in Preterm Infants: Moving from Opioids to Acetaminophen

Preterm infants have many painful moments during their stay in the neonatal nursery.¹ Since the late 1980s, pediatricians and neonatologists have become aware that not treating pain in these infants was not only inhumane but also was associated with negative short- and long-term outcomes. Therefore, both non-pharmacologic and pharmacologic interventions were introduced in the care of the preterm infant during the last 3 decades. The most commonly used drugs to treat pain in these vulnerable infants have been, and still are, opioids such as morphine and fentanyl. However, their use is linked with well-known short-term adverse events such as low blood pressure and respiratory depression. Furthermore, depending on the duration of treatment and the opioid used, tolerance will appear and result in an increased opioid dose to assure continued pain relief. As a consequence, iatrogenic opioid abstinence syndrome may occur after discontinuation of the opioid treatment, resulting in additional discomfort for these preterm infants with a subsequent increase in the duration of their hospital stay.

In adult medicine, the use of intravenous acetaminophen results in a so called “opioid sparing” effect but it is unclear if this also results in less opioid-related side effects.² The same might hold true for the use of acetaminophen in neonates and infants. Recently it was shown that the use of intravenous acetaminophen resulted in significantly less morphine use in neonates and infants undergoing major noncardiac surgery during the first 48 hours after surgery: 121 $\mu\text{g}/\text{kg}$ vs 357 $\mu\text{g}/\text{kg}$.³ Despite this 3-fold decrease in morphine use in the paracetamol group, no difference in adverse events was seen.³ However, without having the assurance that adding intravenous acetaminophen to opioids will result in less opioid-related adverse event, neonatologists have started using intravenous acetaminophen in both term and preterm infants. Thus, the article by Härmä et al⁴ in this issue of *The Journal* is extremely timely and might help in the important discussion on the question whether the use of intravenous acetaminophen in preterm infants is already justified based on our current knowledge. The authors found that the need for morphine decreased significantly in preterm infants of less than 32 weeks after the introduction of acetaminophen. However, to reach a 2-fold reduction in morphine use, almost 17 doses of acetaminophen per patient were needed. Moreover, there were no differences in adverse events detected between the 2 groups. Based on the current available literature in adults, term, and preterm infants, it seems that indeed the use of intravenous acetaminophen will reduce the amount of morphine used in different clinical situations. However, the question remains if acetaminophen used to decrease morphine also improves the overall safety for the patients.

Lessons Learned

Treating pain in preterm infants needs to be based on the right indication and the use of a validated pain assessment tool in combination with an algorithm that clearly delineates the necessary responses of the caregivers if abnormal pain scores are detected. Without pain assessment and a treatment protocol, each preterm infant treated for pain will be essentially enrolled in an uncontrolled and unapproved clinical trial that will not result in any useful data.

If non-pharmacologic treatment of pain is not sufficient, a decision to use a drug in these preterm infants should be made. Most medications administered to preterm infants lack information to support their efficacy and safety and, as a consequence, around 90% of drugs given to preterm infants have not been approved by the Food and Drug Administration. Despite this dreadful situation, there is an imperative to treat pain in these fragile patients. Therefore, the choice of which drug to use is often based on a variety of factors, such as the clinical impression of the drug-prescribing neonatologist about the severity of the pain, studies in older infants, or any pilot data in preterm infants. After the most appropriate drug has been selected, the next step will be to determine the dosing regimen for that specific drug.

Now it gets very dicey as illustrated by the fact that despite the use of opioids for over 25 years in preterm infants, only recently dosing guidelines for preterm infants were established that were appropriately validated.⁵ Until then there has been a large variability in clinical practice resulting in an almost 100-fold variation in dosing regimens. However, for the use of intravenous acetaminophen, the situation is better. There is already a lot of information on the pharmacokinetics of acetaminophen in preterm infants with gestational age more than 28 weeks.⁶ Very recently, more information has become available for infants with gestational ages less than 28 weeks.⁷ In this respect, many lessons have been learned from our earlier experience with morphine.

Less is More?

It seems that we have better information for dosing acetaminophen in our youngest patients but what about safety? It is clear that we need to design trials with sufficient power to determine if the benefits of using a drug exceed the risks.⁸

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In addition to short-term outcome, it will be necessary to conduct long-term follow-up to assure that short-term positive findings do not turn bad in the long run. To be more specific, there are very recent reports on the link between acetaminophen use during pregnancy or in early neonatal life and neurocognitive impairment, including attention-deficit/hyperactivity disorder symptoms at ages 7 and 11 years, or autism spectrum disorder.⁹⁻¹¹

Besides possibilities of short-term toxicity, there are also epidemiologic studies that suggest a link between paracetamol exposure in early infancy and the risk of asthma or other atopy-related diseases, similar to the link between fetal/maternal exposure and atopy in early infancy.¹² There is no causality yet, but as neonatologists we need to realize that we treat preterm infants with medications like acetaminophen during vulnerable periods of development. These exposures are avoided if the infant is still in utero but as soon as the infant is born, concerns about exposure seem to decrease or even disappear.

In summary, there is no doubt that preterm infants with pain deserve adequate pain management. If non-pharmacologic interventions are not sufficiently effective, the use of medications will be necessary. At such moment, whatever drug is chosen, it will have insufficient information on mode of action, the pharmacokinetics, short- and long-term safety, and ease of administration. Besides initiation, protocols for subsequent weaning are also of utmost importance. There is an imperative to design and conduct trials with sufficient power to determine if the drug of choice has more benefits than risks for preterm infants. In general, it is better to use only 1 drug for a certain indication compared with a combination of drugs because the risks of drug-drug interaction will increase with every drug added. Neonates are the last therapeutic orphans but all stakeholders (regulators, industry, academia, parents, etc.) are working to improve that situation. Therefore, there is a huge opportunity at this moment to improve drug treatments of infants. One of the initiatives that has just been launched is the International Neonatal Consortium, an initiative led by the Critical Path Institute.¹³ ■

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